LCCC 1413: De-intensification of Radiation and Chemotherapy for Favorable-Risk HPV-related Oropharyngeal Squamous Cell Carcinoma

NCT02281955

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Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: Departments of Radiation Oncology University of North Carolina and University of Florida

Other participating institutions: University of Florida, Gainesville, FL; Rex Healthcare, Raleigh, NC; High Point Regional Health, High Point, NC; Pardee Memorial Hospital, Hendersonville, NC

Version Date: 12/19/2016

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Bhishamjit Chera, M.D.

PI Signature: _____

Date: December 19, 2016

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

The proposed study is a follow-up study to LCCC 1120. In LCCC 1120, patients with HPV positive and/or p16 positive low-risk oropharyngeal squamous cell carcinoma (OPSCC) received de-intensified chemoradiotherapy (CRT) followed by a limited surgical evaluation. The primary endpoint of LCCC 1120 was the rate of pathological complete response (pCR) after CRT. Power computations were performed for N=40 and were based on the null hypothesis (H0) that the pCR for de-intensified chemoradiotherapy is at least 87%, the historical rate. The type 1 error for this calculation was 14.2%. 43 patients enrolled and 38 were evaluable for the primary endpoint. The observed pCR rate was 89% (34/38). Since the observed pCR rate was excellent in LCCC 1120 and was in concordance with the expected rate, in the proposed study we will not mandate a post-CRT surgical evaluation. Instead a PET/CT 10 to 16 weeks post-CRT will be used to determine whether a surgical evaluation is needed. This study will be multi-institutional, with patients also enrolling at the University of Florida, Gainesville, Florida; Rex Cancer Center of Raleigh, Raleigh, North Carolina; High Point Regional Health, High Point, North Carolina; and Pardee Memorial Hospital, Hendersonville, North Carolina.

1.2 Standard of care CRT for OPSCC

The standard treatment regimen for HPV-associated oropharyngeal or unknown primary squamous cell carcinoma of the head and neck is 70 Gy, 2 Gy per day, 35 fractions, over 7 weeks with 2 to 3 doses of cisplatin 100mg/m^2. Most institutions perform a PET/CT at 10 to 16 weeks after CRT to assess response. Depending on the clinical response, patients may have to have a biopsy of the primary site and/or a neck dissection after treatment. Typically patients with a negative PET/CT scan are observed (i.e. no surgery). Standard CRT is associated with significant acute toxicity with most patients experiencing grade 3 and 4 acute toxicity during treatment. Furthermore, approximately 20% of patients will have Grade 3-4 long-term morbidity related to their definitive CRT.

1.3 HPV related OPSCC

The incidence of OPSCC is increasing and is thought to be secondary to HPV infection of the oropharyngeal mucosa[1-8]. Evidence is accumulating that suggests that HPV-positive HNSCC may be a distinct clinical and biological entity. The affected individuals are more likely to be white men, younger than 60 years of age, unmarried, and have a minimal history of alcohol or tobacco use[3,9-30]. HPV-positive HNSCC has a higher response rate to neoadjuvant chemotherapy and in general has a better prognosis to therapy as compared to HPV-negative HNSCC[10,13,18,19,22]. Biologically, the HPV oncoproteins E6 and E7 inactivate the tumor suppressor proteins p53 and pRb, respectively. Inactivation of pRB by E7 leads to upregulation of the p16 tumor suppressor protein. Thus, overexpression of p16 may be regarded as a biomarker for HPV-positive HNSCC[18,29]. Furthermore, HPV-positive HNSCC is more likely to be associated with a wild-type p53, unlike tobacco-induced HNSCC[11]. Because of the observed improved prognosis and distinct molecular profile, some have suggested that HPV-positive tumors

may be more sensitive to CRT. The standard CRT regimen for most HNSCC is 70 Gy with 3 cycles of concurrent cisplatin at 100mg/m2[31]. Less intensive chemotherapy and/or radiation may be just as effective in HPV-related oropharyngeal HNSCC and reduce the severity of acute toxicity and long-term morbidity associated with CRT. We recently completed a phase II study evaluating de-intensified CRT which showed promising results. The proposed study will further study the efficacy of de-intensification.

1.4 Prospective Clinical Data on HPV positive HNSCC

Numerous retrospective studies have shown that patients with HPV-positive HNSCC have a significantly better prognosis than patients with HPV-negative HNSCC[5,25,29]. These preliminary data have been verified in analyses of prospective clinical trials[10,13,18]. Fakhry et al. evaluated the HPV status of 96 patients with laryngeal or oropharyngeal SCC from an Eastern Cooperative Oncology Group (ECOG) phase II trial. Patients with HPV positive tumors had higher response rates after induction chemotherapy (82% vs. 55%, p = 0.01) and CRT (84% vs. 57%, p = 0.007) as compared to those with HPV-negative tumors. The 2 year overall survival was also improved - 95% (HPV positive) vs. 62% (HPV negative). Lassen et al. analyzed the Danish Head and Neck Cancer Group (DAHANCA) 5 trial and observed an improved local-regional control, disease specific survival, and overall survival in patients whose tumors were p16 positive (a surrogate marker for HPV) versus those who were p16 negative[18].

The RTOG 0129 prospective randomized trial also validated HPV positivity as being a strong, independent prognostic factor for overall and progression free survival[10]. RTOG 0129 compared accelerated fractionation radiotherapy with standard fractionation, both with concurrent cisplatin (2 cycles in the former and 3 cycles in the latter). There was no statistical difference in overall or progression free survival between the two arms. Post-hoc analysis of HPV status and outcomes in the OPSCC subset showed a significant improvement in OS (82.4%, vs. 57.1% at 3 year; P<0.001) and PFS in the HPV positive tumors. After accounting for other prognostic factors, HPV positivity conferred a 58% reduction in the risk of death (hazard ratio, 0.42; 95% CI, 0.27 to 0.66). Locoregional control was improved in the HPV-positive tumors; however, distant metastatic control and the rate of second malignancies were similar for both HPV-positive and negative OPSCC subgroups. Through recursive portioning analysis this OPSCC cohort was stratified into low, intermediate, and high risk groups for death (3 year OS of 93%, 70.8%, and 46.2% respectively). The factors used for stratification, in order of importance, were: HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage. To be categorized as having low risk of death, a patient must have a HPV-positive tumor and either have ≤ 10 pack years of tobacco smoking and any N stage or >10 pack years of tobacco smoking and N0-N2a nodal stage.

O'Sullivan et al. conducted a large retrospective study of 899 OPSCCs patients treated at the Princess Margaret Hospital in Toronto, Canada[32]. HPV status was ascertained in 505 (56%): 382 HPV positive and 123 HPV negative. All patients were treated with radiation alone or CRT from 2001 to 2009, with a median follow-up of 3.9 years. Recursive portioning analysis segregated HPV-positive patients into low (T1-3 N0-N2c) and high (T4 or N3) distant metastasis risk: 93% vs. 76% respectively. Furthermore,

smoking > 10 pack years reduced overall survival but did not impact recurrence free survival (local, regional, and distant recurrences) in HPV-positive patients. This suggests that other associated tobacco-related disease may be the reason for decreased survival in HPV-positive smokers vs. HPV-positive non-smokers. Also, the recurrence free survival was excellent (>90%) in low-risk HPV-positive patients with T1-2, N0-1 disease treated with RT alone vs. CRT. Thus the addition of chemotherapy to radiation in this very favorable low-stage subset may not be necessary.

1.5 De-intensification of Treatment

De-intensification of therapy is somewhat of a foreign concept for head and neck oncologists. Historically the clinical outcomes of HNSCC have been dismal, with median 5 year OS for all comers being approximately 50%. Because of the poor outcomes of HNSCC, the treatment paradigm has been to intensify therapy. HPV-positive OPSCC may be a unique clinical/biological entity that is associated with a significantly better prognosis because of a potentially increased sensitivity to CRT and thus amenable to de-escalation of therapy.

Several co-operative groups are conducting trials evaluating the reduction of RT dose after neoadjuvant chemotherapy. The Eastern Cooperative Oncology Group currently is conducting a phase II trial studying reduction of RT dose after neoadjuvant chemotherapy in HPV positive OPSCC[33]. Dana-Farber Cancer Institute is also evaluating a modification of the RT dose after neoadjuvant chemotherapy[34]. By increasing the duration and intensity of chemotherapy they will then de-escalate the radiation dose depending on the response to neoadjuvant chemotherapy. This regimen of treatment is not pure de-intensification because one modality (i.e. chemotherapy) is being intensified so that another (i.e. radiation) can be de-intensified. The overall treatment time is lengthened, thus prolonging the duration of acute toxicities. Furthermore, as a whole, neoadjuvant chemotherapy does not improve outcomes in HNSCC[35]. A meta-analysis has shown that the most effective combination of chemotherapy with RT is concurrent chemoradiotherapy[35]. Another de-escalation strategy may be to reduce the intensity of chemotherapy. Retrospective data from Princess Margaret Hospital suggest that the outcome of HPV-positive OPSCC treated with RT alone may be equivalent to CRT[36]. Our study will evaluate de-intensification of CRT by reducing the amount of both concurrent chemotherapy and radiation therapy, which will result in shortening treatment time by 1 week.

1.6 LCCC 1120: Phase II Study of De-intensification of Radiation and Chemotherapy for Low-Risk HPV-related Oropharyngeal Squamous Cell Carcinoma

We conducted a phase II study evaluating the efficacy of de-intensified radiotherapy in a favorable subgroup of patients with OPSCC. Eligible patients had HPV-positive and/or p16-positive OPSCC, T0 – T3, N0 – N2c, M0, and $\leq$ 10 pack years of smoking. Patients received 60 Gy of Intensity Modulated Radiotherapy (IMRT) with concurrent weekly intravenous cisplatin (30 mg/m^2). Diagnostic imaging (CT and/or MRI) was obtained 4 to 8 weeks after completion of CRT to assess response. All patients had surgical resection of any clinically apparent residual primary tumor or biopsy of the primary site if there was no evidence of residual tumor and underwent a neck dissection to encompass at

least those nodal level(s) that were positive pre-treatment, within 4 to 14 weeks after CRT. The primary endpoint of LCCC 1120 was the rate of pCR. Longitudinal assessments of quality of life and patient reported outcomes were also obtained prior to, during, and after CRT. Power computations were performed for N=40 and were based on the null hypothesis (H0) that the pCR for de-intensified chemoradiotherapy is at least 87%, the historical rate. The type 1 error for this calculation was 14.2%. 43 patients enrolled and 38 were evaluable for the primary endpoint. The observed pCR rate was 89% (34/38), which is excellent and within the expected result for a positive outcome.

1.7 Rationale

Because of the positive results of our initial de-intensification study, we are proposing conducting a similar study with 5 major modifications:

1. Not require surgical evaluation after de-intensified CRT:
Biopsy or surgery of the primary site adds morbidity without value. This assessment is no longer standard practice at most institutions and is not necessary in this setting based on the results of our initial study.

Dissecting the neck adds significant morbidity. Standard practice today is to base the need for neck dissection on the results of 12 week PET-CT scan. We required neck dissection in all node positive cases in the initial study because we had no experience limiting the dose to 60 Gy with positive nodes. Based on the results of our initial study and national practice guidelines, we changed the protocol in the current study to require post CRT neck dissection only in cases where the ~12 week PET-CT is positive for residual adenopathy and there is no evidence of primary site recurrence or distant metastasis.

2. No chemotherapy in the most favorable subgroups:
There are now multiple studies demonstrating very high cure rates with RT alone in patients with stage T1-2, N0-1 OPSCC with and without consideration of HPV or smoking status[32,37]. These data and the results of our initial study strongly suggest that 60 Gy RT alone will be adequate for favorable prognosis cases in our study population. For this reason the current study dictates RT alone in: p16/HPV positive, T0-2, N0-1, ≤ 10 pack years.

3. Expand the study to patients with smoking history of ≤ 30 pack-years with ≥5 years of abstinence from smoking:
Tobacco use is a factor of secondary importance following stage and p16/HPV status. The O'Sullivan data suggests that moderate tobacco use did not affect cancer control rates in HPV-positive patients[32]. In view of the excellent results in our initial study it is logical to expand the inclusion criteria of the current study to patients with a moderate smoking history.

4. Chemotherapy: In our prior study, weekly cisplatin was the mandated chemotherapy regimen. However we were not able to offer our prior study to several patients with low-risk OPSCC because of co-morbidities that precluded the use of cisplatin. There are many

other standardly used weekly chemotherapy regimens. So as to increase patient eligibility, we have expanded the acceptable weekly chemotherapy regimens that may be used in this study. Cisplatin is still the preferred, first choice option.

5. Changing the Primary Objective: In our prior study the primary objective was pCR – since surgery was part of the treatment algorithm. For the proposed study, the primary objective will be the more standard 2 year PFS.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate 2 year PFS after de-intensified CRT in HPV-positive and/or p16 positive favorable-risk OPSCC.

2.2 Secondary Objectives

2.2.1 To assess the 2 year clinical outcomes of local control (LC), regional control (RC), local-regional control (LRC), distant metastasis free survival (DMFS), and overall survival (OS).

2.2.2 To compare head and neck quality of life assessments before, during, and after CRT.

2.2.3 To compare speech and swallowing function before and after CRT.

3.0 ENDPOINTS

3.1 Primary Endpoint

Patients with HPV-positive and/or p16-positive favorable-risk OPSCC will receive de-intensified CRT. The 2 year PFS will be evaluated. Our null hypothesis (H_0) is that the PFS rate is 87% and our alternate hypothesis (H_1) is that the PFS rate is 80%.

3.2 Secondary Endpoints

3.2.1 Clinical Outcomes: Kaplan Meier estimates of LC, RC, LRC, DMFS, and OS will be calculated.

3.2.2 Quality of Life: EORTC QLQ 35 (head and neck cancer), EORTC QLQ C30 (general cancer), and depression/anxiety instruments will be administered prior to CRT, during weeks 3 and 6 of CRT, 10 to 16 weeks after CRT, at least every 6 months during the first 2 years after CRT, and annually thereafter. These data will be obtained for descriptive purposes.

3.2.3 Speech and Swallowing: Speech and Swallowing assessments (EAT-10 questionnaire) will be performed prior to CRT and 10 to 16 weeks after CRT, at least every 6 months during the first 2 years after CRT, and annually thereafter. These data will be obtained for descriptive purposes.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 ≥ 18 years of age (no upper age limit)

4.1.2 T0-3, N0 to N2c, M0 squamous cell carcinoma of the oropharynx

4.1.3 Biopsy proven squamous cell carcinoma that is HPV and/or p16 positive

4.1.4 ≤ 10 pack-years smoking history or ≤ 30 pack-years smoking history WITH ≥ 5 years abstinence from smoking

4.1.5 Radiologic confirmation of the absence of hematogenous metastasis within 12 weeks prior to treatment; at a minimum, chest x-ray is required. CT imaging of the chest or PET/CT is acceptable.

4.1.6 ECOG Performance Status 0-1

4.1.7 CBC/differential obtained within 8 weeks prior to treatment, with adequate bone marrow function defined as follows:

4.1.7.1 Platelets ≥ 100,000 cells/mm3

4.1.7.2 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

4.1.8 Adequate renal and hepatic function within 4 weeks prior to treatment, defined as follows:

4.1.8.1 Serum creatinine < 2.0 mg/dl

4.1.8.2 Total bilirubin < 2 x the institutional ULN

4.1.8.3 AST or ALT < 3 x the institutional ULN.

Note that physician attestation of patient having no known history of liver disease can take the place of bilirubin and AST/ALT labs.

4.1.9 Negative pregnancy test within 2 weeks prior to treatment for women of childbearing potential

4.1.10 Women of childbearing potential and male participants who are sexually active must practice adequate contraception during treatment and for 6 weeks following treatment.

4.1.11 Patients must be deemed able to comply with the treatment plan and follow-up schedule.

4.1.12 Patients must provide study specific informed consent prior to study entry

4.2 Exclusion Criteria

4.2.1 Prior history of radiation therapy to the head and neck

4.2.2 Prior history of head and neck cancer.

4.2.3 Unresectable disease (e.g. immobile node on physical exam, nodal disease that radiographgically involves the carotid arteries, nerves)

4.2.4 Currently taking Disease Modifying Rheumatoid Drugs (DMRDs)

4.2.5 Severe, active co-morbidity, defined as follows:

4.2.5.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

4.2.5.2 Transmural myocardial infarction within the last 6 months

4.2.5.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

4.2.5.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

4.2.5.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; Note, however, coagulation parameters are not required for entry into this protocol.

4.2.5.6 Pre-existing ≥ grade 2 neuropathy

4.2.5.7 Prior organ transplant

4.2.5.8 Systemic lupus

4.2.5.9 Psoriatic arthritis

4.2.6 Known HIV positive. HIV positive patients are known to have worse clinical outcomes especially for local, regional, and distant cancer control. This poorer prognosis is thought to be secondary to a compromised immune system. Thus, de-escalation of radiation and chemotherapy is not justifiable.

5.0 STUDY PLAN

5.1 Schema

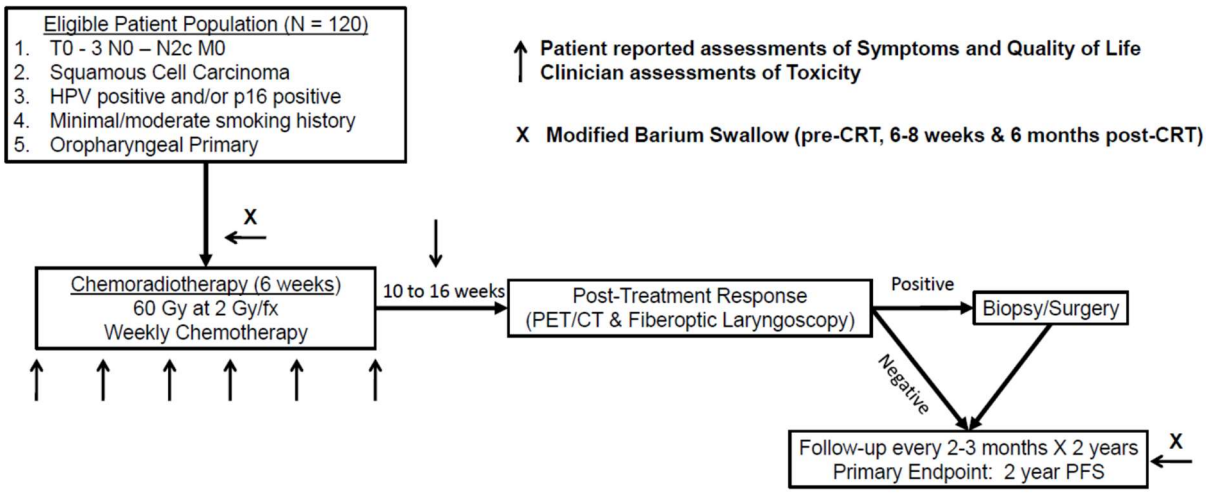

Figure 1: Schema

Figure 1: The primary objective of this study is to assess the 2 year PFS of HPV-related favorable-risk OPSCC after de-intensified CRT. Chemotherapy will not be given to patients with T0-2 N0-1 disease, ≤ 10 pack years smoking history.

5.2 Pretreatment Evaluations: All patients will have standard of care evaluation and staging procedures.

5.2.1 Complete history and physical exam including weight and performance status.

5.2.2 Completion of panendoscopy with directed biopsies and bilateral tonsillectomies if the primary is unknown is strongly recommended, but not required.

5.2.3 Completion of the following radiological studies: at least contrasted neck CT and chest x-ray. Chest CT, PET/CT and/or MRI are optional studies. CT of the neck should have IV contrast unless contraindicated (allergy or adverse reaction or renal issues). PET/CT is satisfactory and can be done instead of or in addition to contrasted neck CT and chest x-ray. Pretreatment ultrasound evaluation with possible FNA is permissible to stage the neck prior to treatment.

5.2.4 Complete dental evaluation is recommended.

5.2.5 Completion of the following laboratory studies: CBC, serum chemistries, liver function tests, and pregnancy test if female.

5.3 HPV and p16 testing

HPV and p16 testing will be performed via fluorescence in-situ hybridization and immunohistochemistry, respectively. Methods and techniques for these tests have been

established by the UNCH, UF, and Rex Cancer Center of Raleigh Departments of Pathology and these biomarkers are already routinely examined for all head and neck tumor specimens obtained at these institutions. This testing may be performed on FNA tissue obtained from a neck node.

5.4 Radiation Therapy

All patients will receive Intensity Modulated Radiotherapy Treatments (IMRT). Tomotherapy is allowed.

5.4.1 CT simulation: CT simulation will be obtained with IV contrast for treatment planning purposes for all patients. The head and neck area will be immobilized with an aquaplast mask. Patients will be positioned in the neck extended position.

5.4.2 Target and Organ at Risk Volumes:

5.4.2.1 Gross Tumor Volume (GTV): is defined as all known gross disease determined on the CT simulation scan.

5.4.2.2 High Risk Clinical Target Volumes (CTV-HR): is defined as the GTV plus a non-uniformly expanded 5 to 10 mm to account for high risk areas of microscopic spread. For situations where the primary tumor was removed with the biopsy (e.g. tonsillectomy) and the primary tumor cannot be seen on radiographic imaging the biopsy site will be included in the CTV-HR. For patients with an unknown primary (T0) the ipsilateral oropharynx (base of tongue, tonsil, soft palate) will be included in the CTV-HR volume.

5.4.2.3 Standard Risk Clinical Target Volume (CTV-SR): is defined as the elective nodal regions. The consensus guidelines for the node negative and node positive necks published by Gregoire et al. will be used as a guide to define the CTV-SR[38,39]. For the situation of the unknown primary (i.e. T0), the nasopharynx will be included in the CTV-SR. The following guidelines will be used in delineating the CTV-SR.

5.4.2.3.1 *Node positive hemi-neck (ipsilateral or contralateral to the primary site)[38]:* The following elective nodal regions should be included in the CTV-SR: Levels Ib-V and retropharyngeal. The cranial extent to the base of skull of Level II and retropharyngeal nodes should be electively irradiated.

5.4.2.3.2 *Ipsilateral node negative hemi-neck[39]:* The following elective nodal regions should be included in the CTV-SR: Levels II –IV and retropharyngeal area. The cranial extent to the base of skull of Level II and retropharyngeal nodes should be electively irradiated.

5.4.2.3.3 *Contralateral node negative hemi-neck[39]:* The contralateral parotid may be spared by omitting irradiation of the cranial portion of Level II and retropharyngeal region, defined as the Level II, retropharyngeal region above the transverse process of the C1 vertebrae and/or where the posterior belly of

the digastric muscle crosses over the jugular vein. Contralateral neck irradiation may be completely omitted for well lateralized tonsil cancers, defined as having no invasion of the base of tongue, and minimal invasion of the soft palate (i.e. > 1 cm from the uvula)[40].

5.4.2.3.4 *Unknown Primary:* The above elective nodal irradiation guidelines will be used. Furthermore the nasopharynx will be included in the CTV-SR.

5.4.2.4 Planning Target Volumes (PTV): To account for daily setup errors, the CTV-HR will be expanded uniformly by 3 mm to create a High Risk Planning Target Volume (PTV-HR). The CTV-SR will be expanded uniformly by 3 mm to create a Standard Risk Planning Target Volume (PTV-SR).

5.4.2.5 Organs at Risk (OAR): The following normal tissues will be segmented on CT simulation scan: spinal cord, brainstem, parotids, cochleae, and larynx.

5.4.2.6 Planning Risk Volumes (PRV): OAR(s) will be uniformly expanded 3mm to create individual Planning Risk Volumes (PRV).

5.4.3 Dose Specification: Dose painting IMRT will be used and all doses will be specified to the PTV. The PTV-HR and PTV-SR will be treated to the following respective total doses: 60 Gy and 54 Gy. The dose per fraction to the PTV-HR and PTV-SR will be 2 Gy per day and 1.8 Gy per day respectively. Thus the total number of fractions will be 30. All fields will be treated once a day Monday through Friday.

5.4.4 IMRT Treatment Planning: PTV's and PRV will be included in the IMRT optimization. Seven to nine equidistant fields will be placed around the PTV. None of the beams will directly oppose one another. Dose objectives will be chosen for the IMRT optimization based on previous institutional experience. Dose painting (i.e. simultaneous integrated boost) will be used to create one IMRT plan. The PTV-SR contours will encompass the PTV-HR contours. The dose to the PTV-SR plan will be 54 Gy at 1.8 Gy per daily fraction in 30 fractions. The PTV-HR will be treated to 60 Gy at 2 Gy per daily fraction in 30 fractions. IMRT to treat the entire neck is preferred, however a matched low anterior neck field technique may be used only if it does not result in significant dose heterogeneity for the PTV-HR.

The historical, standard radiation dose for definitive treatment of squamous cell carcinoma of the head and neck is 70 Gy. Historically 70 Gy at 2 Gy per daily fraction is given to the gross tumor and 50 Gy at 2 Gy per daily fraction is given to areas at risk for harboring subclinical microscopic disease. 70 Gy is also the standard dose for HPV positive head and neck cancer. 70 Gy is the standard radiation dose in both study arms of the currently ongoing RTOG 1016 (Phase III trial of Radiotherapy plus Cetuximab versus Chemoradiotherapy in HPV-asssociated Oropharynx Cancer). In the proposed study we will be giving 60 Gy at 2 Gy per daily fraction to the gross tumor and 54 Gy at 1.8 Gy per daily fraction to areas at risk for harboring subclinical microscopic disease. Thus the proposed dose in our study is actually lower than historical standards and the current RTOG study.

5.4.5 Dose Constraints

- PTV-HR and PTV-SR
  - 100% of the prescription should cover 95% of the PTV
  - No more than 20% of the PTV should receive ≥ 110% of the prescribed dose
  - No more than 1% of the PTV should receive ≤ 93% of the prescribed dose
- Non-target Tissue
  - No more than 1% of the tissue outside the PTV should receive ≥ 110% of the prescribed dose
- PRV
  - Spinal Cord: 0.1cc ≤ 50 Gy
  - Brainstem: 0.1cc ≤ 54 Gy
  - Parotid: Mean dose < 26 Gy and/or 50% < 30 Gy
  - Cochlea: Mean dose < 45 Gy
  - Larynx: Mean dose < 41 Gy and/or 60 Gy to < 20%

PTV coverage should not be compromised to meet the dose constraints of the parotid, cochlea, or larynx. Sparing of these structures is left at the discretion of the treating radiation oncologists. The dose constraints for the spinal cord and brainstem must be satisfied. This may be done at the cost of altering the PTV.

5.4.6 Treatment Verification: Weekly orthogonal films or cone beam CT's should be performed to verify patient setup (at least).

5.4.7 Radiation Treatment Breaks: Ideally, treatment breaks, if necessary, should not exceed 5 treatment days at a time and 10 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons.

5.5 Chemotherapy: In our initial study, LCCC 1120, all patients were started on a regimen of cisplatin 30mg/m^2 given intravenously over 60 minutes weekly during IMRT; 6 total doses for a total of 180 mg/m^2. However, if cisplatin was not tolerated, it was permissible to switch to alternative, acceptable weekly chemotherapy regimens such as cetuximab, carboplatin, or carboplatin/taxol. For the proposed study, cisplatin is the preferred mandated first choice chemotherapy, however alternative weekly regimens are permissible. Typical reasons for a patient not being able to receive cisplatin include renal insufficiency and history of hearing loss. Justification for not using cisplatin must be documented. Analysis of a prospective national registry, Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN), showed that the three most commonly prescribed concurrent (with radiation) regimens (in order) are single agent cisplatin (51%), single-agent cetuximab (21%), and carboplatin plus paclitaxel (7%). Single agent carboplatin was infrequently used (3%) (Wong et al. Cancer 2011;117:1679–86.). The acceptable weekly chemotherapy regimens that may be used on this study are the following:

- Cisplatin 30 to 40 mg/m^2 (preferred, first choice)
- Cetuximab 250mg/m^2 (preferred, second choice)
- Carboplatin AUC 1.5 and paclitaxel 45 mg/m^2 (preferred, third choice)

- Carboplatin AUC 3 (preferred, fourth choice)

Chemotherapy will be given intravenously weekly during IMRT. 6 total doses will be given. It is preferred that the doses be administered on days 1, 8, 15, 22, 29, and 36; however, this is not mandatory. ***Chemotherapy will not be given to patients with T0-2 N0-1 disease, ≤ 10 pack years smoking history.***

5.5.1 Dose Modifications for chemotherapy: Because of the low weekly dosage of chemotherapy, we anticipate few dose modifications secondary to acute toxicities. Dose modifications are allowed and will be directed by the treating medical oncologist according to his/her discretion on an individual patient basis.

5.5.2 Changing Chemotherapy Regimens: In the event that cisplatin is held for 1 week and the patient is still deemed unable to receive further weekly cisplatin (because of cisplatin-related toxicity), patient will be switched to another protocol-acceptable weekly chemotherapy regimen (cetuximab, carboplatin/taxol, or carboplatin).

Other changes may be done on a case-by-case basis depending on the standard of practice of the treating medical oncologist.

5.6 Post-Chemoradiotherapy Assessment of Clinical Response

PET/CT will be performed 10 to 16 weeks (optimally at week 12) after CRT to assess response. All patients will be evaluated via clinical exam and fiberoptic laryngoscopy by the radiation oncologist and head and neck surgeon around the same time as the PET/CT scan. Note that the fiberoptic laryngoscopy need only be done once, at either 6 or 12 weeks post-CRT, with additional laryngoscopy procedures performed at the discretion of the physician. Decisions for surgical evaluation will be based on the results of the PET/CT and clinical exam at that time. Other optional imaging studies may be performed (e.g. CT scan 4 to 6 weeks after completion of CRT).

5.7 Surgery after CRT

Patients with a positive PET/CT scan will undergo surgical evaluation at the discretion of the surgeon. This may include biopsies and/or oncological resections of the primary tumor and lymph node metastases. The type of surgical procedure will be left to the discretion of the surgeon however the goal will be to remove any suspected residual tumor with a negative resection margin while maintaining organ preservation. Patients with a negative PET/CT scan will be observed.

5.8 Other Therapy

5.8.1 Permitted Supportive Therapy: All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol

5.8.1.1 Antiemetics: Prophylactic antiemetics and supportive therapy for nausea and vomiting are permitted and highly recommended in patients participating in

this study. These interventions should be made according to institutional guidelines.

5.8.1.2 Nutritional Supplementation: Close monitoring of patients' volume status and body weight is strongly recommended. Nutritional supplementation through a nasogastric or gastrostomy feeding tube should be considered in patients who are unable to maintain hydration or experience more than 10% loss of body weight due to mucositis.

5.8.2 Non-permitted Supportive Therapy

5.8.2.1 Hematopoietic Growth Factors: Hematopoietic growth factors are not permitted during radiation therapy. Growth factors are only permitted if administered after radiation therapy has been completed. Erythropoiesis stimulating agents are not permitted.

5.8.3 Other Supportive Care Clinical Studies: Patients will be allowed to participate in other supportive care clinical studies that do not interfere with the treatment plan of the current study.

5.9 Patient Assessments

5.9.1 Quality of Life (QOL) and Patient-Reported Outcomes (PRO)

Patients will be offered the opportunity to participate in QOL and PRO assessments. QOL and PROs will be assessed prior to CRT, during weeks 3 and 6 of CRT, 10 to 16 weeks after completion of CRT, at least every 6 months during the first 2 years after CRT, and annually thereafter. The study coordinator will administer the QOL and PRO assessments.

5.9.1.1 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30: The EORTC QLQ-C30 (Appendix) is a core questionnaire that is a reliable and valid measure of the quality of life of cancer patients in the clinical research setting. It incorporates nine multi-item scales: five function scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included[41].

5.9.1.2 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-H&N35: The EORTC QLQ-H&N35 (Appendix) is a questionnaire designed to assess the quality of life of head and neck (H&N) cancer patients in conjunction with the general cancer-specific EORTC QLQC30. The QLQ-H&N35, in conjunction with the QLQ-C30, provides a valuable tool for the assessment of health-related

quality of life in clinical studies of H&N cancer patients before, during, and after treatment with radiotherapy, surgery, or chemotherapy[42].

5.9.1.3 Patient Reported Outcomes version of the CTCAE: A subset of items pertinent to HNC will be drawn from the PRO-CTCAE system. 25 to 30 items will be used to evaluate the presence and/or severity of range of symptoms, as well as the degree to which symptom/toxicity interferes with usual function.

5.9.2 Speech and Swallowing Evaluations

All patients will have modified barium swallow and/or Fiberoptic endoscopic evaluation of swallowing (FEES) studies prior to CRT, and 6-8 weeks and 6 months after completion of CRT. The Rosenbek Penetration Aspiration Scale (Appendix) will be used to quantify dysphagia[43]. Furthermore the Eating Assessment Tool (EAT-10) will be administered prior to CRT, 10-16 weeks after completion of CRT, at least every 6 months during the first 2 years after CRT, and annually thereafter. EAT-10 (Appendix) is a self-administered, symptom specific outcome instrument for documenting dysphagia severity[44].

5.9.3 Monitoring of Acute and Chronic Toxicities

The NCI-CTCAE v4.0 criteria will be used to document acute and late adverse events/toxicities associated with CRT. These assessments will be done by the physician on the same schedule as the QOL and PRO assessments as indicated in Section 5.9.1.

5.10 Duration of Study

The primary endpoint of this study is to evaluate the 2 year PFS rate after de-intensified CRT in HPV-positive and/or p16 positive OPSCC. Patient participation concludes after 2 years of follow-up after completion of CRT. However, patients will continue long-term routine follow-up as is our institutional policy and will be asked to continue QOL and PRO parts of the study, as well as the EAT-10.

5.11 Duration of Follow Up

After completion of treatment patients will be followed according to our institutional standard practice: clinical evaluations every 2 to 3 months for 2 years, every 6 months for 3 additional years, then yearly thereafter. As part of routine surveillance patients will receive chest imaging every 6 months for 2 years then yearly thereafter and thyroid function studies will be checked every 6 months for 2 years then yearly thereafter.

Our routine standard practice for all of our head and neck cancer patients is to encourage post-treatment dental follow-up and care. This study does not increase the need for post-treatment dental care or increase the risk of dental complication. In fact it may decrease the risk/incidence of post-treatment dental complications because the radiation dose is being reduced to 60 Gy. Thus we will continue to practice our routine post-treatment dental care recommendations.

See the Time and Events Table in the Appendix for a summary of the patient assessments/procedures and time periods.

6.0 ADVERSE EVENTS

6.1 Definition

An adverse experience is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse experience or event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

In this study, toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.2 Reporting

Patients will be receiving radiation, chemotherapy, and surgical treatments within the accepted standard of care. We expect patients to experience the known toxicities that are associated with these standard treatments. In the recently published RTOG 0129 study the overall rate of grade 3 or 4 acute toxic events was approximately 80% and the late grade 3 or 4 toxic events was approximately 25%. Because we are de-intensifying the CRT by reducing the total dose of radiation to 60 Gy and administering Cisplatin 30mg/m2 weekly (RTOG 0129 treated patients with at least 70 Gy of radiation and 2 cycles of 100mg/m2 of cisplatin) the acute and late toxicities should not be greater than what has been historically observed.

Affiliate Sites

For all Grade 3 and above toxicities which occur to any patient in the course of their treatment on this study or following cessation of treatment, all Affiliate sites must inform the Study Coordinator within 24 hours of learning of its occurrence. The study coordinator will record the toxicities and report them to the DSMC at the time of scheduled reviews. Toxicities classified as unexpected, related to a subject's participation in the research, and suggesting that the research places subjects or others at a greater risk of harm than was previously known will be reported to the IRB.

6.3 Grade 3 and above toxicities which occur to any patient in the course of their treatment on this study or following cessation of treatment will be recorded by the Study Coordinator and reported to the DSMC at the time of scheduled reviews. Toxicities classified as serious, unexpected, AND related to treatment will be reported to the IRB. Treatment of Adverse Event

Patients who develop any adverse event while on study will receive standard of care treatment. Radiation, cisplatin, and surgery are already standard of care treatments for these patients. Standard of care treatment for known potential adverse events from these treatments are established.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design/Study Endpoints

The main objective of this Phase-II trial is to estimate the two-year progression-free survival probability (PFSP) in this group of patients treated with de-escalated radiotherapy. The planned total sample size is 120 patients. The recruitment phase is expected to last 24 to 36 months, with 40 to 60 patients accrued each year. A minimum follow up of two years per subject implies a total study duration of 4 to 5 years. Drop out is expected to be about 10%, based on a previous trial (LCCC 1120), hence we expect a total of 108 patients to complete the study.

The statistical aim is phrased as a hypothesis test with the null hypothesis being that the two-year PFSP is 0.87 and the alternative hypothesis being that the two-year PFSP is 0.80 (or less). If the null hypothesis is rejected the conclusion will be that the de-escalated treatment is inferior to the standard treatment. If the null hypothesis is not rejected the conclusion will be that the de-escalated treatment is at least as good as the standard RT.

For a sample size of 108 patients who complete the study, the null hypothesis will be rejected if 21 or more patients fail. The same rejection rule applies for sample sizes from 107 to 111, with Type-I error from 0.034 at n=107 to 0.049 at n=111. For n=112 to 117 the null will be rejected if 22 or more patients fail, with Type-I error .031 to .047. Failure is defined as not reaching the two-year time point progression-free. Defining P(Reject H0) to be the probability of rejecting the null hypothesis, the performance of the test, with 108 patients who complete the study, is summarized in the following table.

True 2-year PFSP	P(Reject H0)
0.87	0.04
0.80	0.60
0.77	0.84
0.75	0.93

7.2 Data Analysis Plan

The main hypothesis test will be performed as described above. Additionally, a Kaplan-Meier curve will be estimated for PFS, local control, regional control, local-regional control, distant metastasis free survival and overall survival. Head and neck quality of life assessments, patient reported symptoms and speech and swallowing functions before during, and after CRT will be compared, using the paired t-test or McNemar's test as appropriate.

In addition to the above, other exploratory analyses utilizing study-related data may be performed.

7.3 Safety Meetings

The principal investigator will provide continuous monitoring of patient safety in this study with periodic reporting to the Data Safety Monitoring Subcommittee (DSMS).

The principal investigator will submit summaries, together with formatted reports, to the DSMS for review. The reports will be reviewed at the time of the appointed meeting schedule established by this committee. Following review, the DSMS will report its recommendations, together with the principal investigator report, to the Oncology PRC. These reports will be reviewed by the PRC at the time of the study's annual IRB renewal. When warranted, the PRC and/or DSMS will have the prerogative to request additional information.

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment into this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form
- Executed clinical research contract

8.3 Registration Procedures

All patients must be registered with the Study Coordinators at the Departments of Radiation Oncology at the University of North Carolina, the University of Florida, Rex Cancer Center of Raleigh, High Point Regional Health, and Pardee Memorial Hospital before enrollment in the study. For both UNC and Affiliate patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator.

8.4 Data Management and Monitoring/Auditing

The University of North Carolina will serve as the coordinating center for this trial. All data will be collected, entered, and maintained in secured servers in the Departments of Radiation Oncology at the University of North Carolina, the University of Florida, Rex Cancer Center of Raleigh, High Point Regional Health, and Pardee Memorial Hospital by the Study Coordinators. De-identified, password protected data from patients enrolled at the University of Florida, Rex Cancer Center of Raleigh, High Point Regional Health, and Pardee Memorial Hospital will be electronically submitted to the Department of Radiation Oncology at the University of North Carolina via a secured computer server. The data will be pooled at UNC where personnel there will coordinate and manage data for quality control assurance and integrity. Data analysis will take place at UNC as well. As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six months.

8.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

<u>For Institutions Relying on UNC's IRB:</u>

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNC Study Coordinator).

8.5.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNC Study Coordinator by facsimile or via email within 10 business days after the original submission.

8.5.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the UNC IRB. According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: Affiliate personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNC Study Coordinator within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNC Study Coordinator.

8.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNC Study Coordinator prior to submission to their IRB.

8.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and

regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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10. APPENDIX

Eligibility Checklist

LCCC 1413- DE-INTENSIFICATION OF RADIATION AND CHEMOTHERAPY FOR FAVORABLE-RISK HPV-RELATED OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

STUDY ELIGIBILITY CHECKLIST

Subject: _____
MRN: _____
Study ID #: _____

Inclusion Criteria:

- ☐ (Y) ≥ 18 years of age
- ☐ (Y) T 0-3, N0 to N2c, M0 squamous cell carcinoma of the oropharynx
- ☐ (Y) Biopsy proven squamous cell carcinoma that is HPV and/or p16 positive
- ☐ (Y) ≤ 10 pack-years smoking history or ≤ 30 pack-years smoking history WITH ≥ 5 years abstinence from smoking
- ☐ (Y) Radiologic confirmation of the absence of hematogenous metastasis within 12 weeks prior to treatment; at a minimum, chest x-ray is required. CT imaging of the chest or PET/CT is acceptable.
- ☐ (Y) ECOG Performance Status 0-1
- ☐ (Y) CBC/differential obtained within 8 weeks prior to treatment, with adequate bone marrow function defined as follows:
  Platelets ≥ 100,000 cells/mm3 **Value:** _____
  Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.) **Value:** _____
- ☐ (Y) Adequate renal and hepatic function within 4 weeks prior to treatment, defined as follows:
  Serum creatinine < 2.0 mg/dl **Value:** _____
  Total bilirubin < 2 x the institutional ULN **Value:** _____
  AST or ALT < 3 x the institutional ULN **Value:** _____
  Note that physician attestation of patient having no known history of liver disease can take the place of bilirubin and AST/ALT labs. Please note that here.
- ☐ (Y) Negative pregnancy test within 2 weeks prior to treatment for women of childbearing potential
- ☐ (Y) Women of childbearing potential and male participants who are sexually active must practice adequate contraception during treatment and for 6 weeks following treatment.
- ☐ (Y) Able to comply with the treatment plan and follow-up schedule
- ☐ (Y) Study-specific informed consent provided prior to study entry

Exclusion Criteria:

- ☐ (N) Prior history of radiation therapy to the head and neck
- ☐ (N) Prior history of head and neck cancer
- ☐ (N) Unresectable disease (e.g. immobile node on physical exam, nodal disease that radiographgically involves the carotid arteries, nerves)
- ☐ (N) Currently taking Disease Modifying Rheumatoid Drugs (DMRDs)
- ☐ (N) Unstable angina and/or congestive heart failure requiring hospitalization within last 6 months
- ☐ (N) Transmural myocardial infarction within last 6 months
- ☐ (N) Acute bacterial or fungal infection requiring intravenous antibiotics at time of registration
- ☐ (N) Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- ☐ (N) Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
- ☐ (N) Pre-existing $\geq$ grade 2 neuropathy
- ☐ (N) Prior organ transplant
- ☐ (N) Systemic lupus
- ☐ (N) Psoriatic arthritis
- ☐ (N) Known HIV Positive

_____ _____

Attending Physician Signature Date

EORTC QLQ-C30[34]

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ-H&N35[35]

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		**No**	**Yes**
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

PRO-CTCAE

NCI- PRO-CTCAE ITEMS

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⓧ in the one box that best describes your experiences over the past 7 days…

FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

DECREASED APPETITE				
What was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

ARM OR LEG SWELLING				
How OFTEN did you have ARM OR LEG SWELLING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

LOOSE OR WATERY STOOLS (DIARRHEA)				
How OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

NAUSEA				
How OFTEN do you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

VOMITING				
How OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

NUMBNESS OR TINGLING IN YOUR HANDS OR FEET				
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

BLURRY VISION				
What was the SEVERITY of your BLURRY VISION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did BLURRY VISION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

SHORTNESS OF BREATH				
What was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much does your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

HAIR LOSS				
Did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

RASH	
Did you have any RASH?	
O Yes	O No

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

DEPRESSION				
How OFTEN did you have SAD OR UNHAPPY FEELINGS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your SAD OR UNHAPPY FEELINGS?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did SAD OR UNHAPPY FEELINGS INTEFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

INSOMNIA INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY				
What was the SEVERITY of your INSOMNIA INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did your INSOMNIA INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

PAIN				
How OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

EXPECTED MENSTRUAL PERIOD		
Did you miss an EXPECTED MENSTRUAL PERIOD?		
O Yes	O No	O Not applicable

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)				
How OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

ACHING MUSCLES				
How OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did ACHING MUSCLES INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

ACNE OR PIMPLES ON THE FACE OR CHEST				
What was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

PROBLEMS WITH TASTING FOOD OR DRINK				
What was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

CONSTIPATION				
What was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

COUGH				
What was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much does your COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

DECREASED SEXUAL INTEREST				
What was the SEVERITY of your DECREASED SEXUAL INTEREST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

UNEXPECTED DECREASE IN SWEATING	
Did you have an UNEXPECTED DECREASE IN SWEATING?	
O Yes	O No

DIFFICULTY GETTING OR KEEPING AN ERECTION						
What was the SEVERITY of your DIFFICULTY GETTING OR KEEPING AN ERECTION at its WORST?						
O None	O Mild	O Moderate	O Severe	O Very severe	O Not sexually active	O Prefer not to answer

BLOATING OF THE ABDOMEN				
How OFTEN did you have BLOATING OF THE ABDOMEN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your BLOATING OF THE ABDOMEN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

BODY ODOR				
What was the SEVERITY of your BODY ODOR at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

BREAST AREA ENLARGEMENT OR TENDERNESS				
What was the SEVERITY of your BREAST AREA ENLARGEMENT OR TENDERNESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

BRUISE EASILY (BLACK AND BLUE MARKS)	
Did you BRUISE EASILY?	
O Yes	O No

CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS	
Did you have any CHANGE IN COLOR OF YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

DIFFICULTY SWALLOWING				
What was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

DIZZINESS				
What was the SEVERITY of your DIZZINESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DIZZINESS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

DRY MOUTH				
What was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

DRY SKIN				
What was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

EJACULATION PROBLEMS					
How often did you have EJACULATION PROBLEMS?					
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly	O Prefer not to answer

ANXIETY				
How OFTEN did you feel ANXIETY?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ANXIETY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did ANXIETY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NOTHING WOULD CHEER YOU UP				
How OFTEN did you feel that NOTHING WOULD CHEER YOU UP?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your feelings that NOTHING WOULD CHEER YOU UP at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did feeling that NOTHING WOULD CHEER YOU UP INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

FLASHING LIGHTS IN FRONT OF YOUR EYES	
Did you have any FLASHING LIGHTS IN FRONT OF YOUR EYES?	
O Yes	O No

HAND-FOOT SYNDROME(A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS, OR PAIN)				
What was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

HEADACHE				
How OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

HEARTBURN				
How OFTEN did you have HEARTBURN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your HEARTBURN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

HICCUPS				
How OFTEN did you have HICCUPS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your HICCUPS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

HIVES (ITCHY RED BUMPS ON THE SKIN)	
Did you have any HIVES (ITCHY RED BUMPS ON THE SKIN)?	
O Yes	O No

HOT FLASHES				
How OFTEN did you have HOT FLASHES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your HOT FLASHES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

URINATE FREQUENTLY					
Were there times when you had to URINATE FREQUENTLY?					
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly	O Not Applicable
How much did your FREQUENT URINATION INTERFERE with your usual or daily activities?					
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much	

URGE TO URINATE					
How OFTEN did you feel an URGE TO URINATE ALL OF A SUDDEN?					
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly	O Not Applicable
How much did SUDDEN URGES TO URINATE INTERFERE with your usual or daily activities?					
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much	O Not Applicable

INCREASED SKIN SENSITIVITY TO SUNLIGHT	
Did you have any INCREASED SKIN SENSIVITY TO SUNLIGHT?	
O Yes	O No

INCREASED PASSING OF GAS (FLATULENCE)	
Did you have any INCREASED PASSING OF GAS (FLATULENCE)?	
O Yes	O No

IRREGULAR MENSTRUAL PERIODS		
Did you have any IRREGULAR MENSTRUAL PERIODS?		
O Yes	O No	O Not Applicable

ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

LOSE CONTROL OF BOWEL MOVEMENTS					
How OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?					
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly	O Not Applicable
How much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?					
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much	O Not Applicable

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

LOSS OF CONTROL OF URINE (LEAKAGE)					
How OFTEN did you LOSS OF CONTROL OF URINE (LEAKAGE)?					
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly	O Not Applicable
How much did LOSS OF CONTROL OF URINE (LEAKAGE) INTERFERE with your usual or daily activities?					
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much	O Not Applicable

FINGERNAILS OR TOENAILS	
Did you lose any FINGERNAILS OR TOENAILS?	
O Yes	O No

MOUTH AND THROAT SORES				
What was the SEVERITY of your MOUTH AND THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did MOUTH AND THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NOSEBLEEDS				
How OFTEN did you have NOSEBLEEDS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NOSEBLEEDS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

PAIN DURING VAGINAL SEX						
What was the SEVERITY of your PAIN DURING VAGINAL SEX at its WORST?						
O None	O Mild	O Moderate	O Severe	O Very severe	O Not sexually active	O Prefer not to answer

PAIN IN THE ABDOMEN (BELLY)				
How OFTEN did you have PAIN IN THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN IN THE ABDOMEN (BELLY) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

PAIN OR BURNING WITH URINATION					
What was the SEVERITY of your PAIN OR BURNING WITH URINATION at its WORST?					
O None	O Mild	O Moderate	O Severe	O Very severe	O Not Applicable

PAIN, SWELLING, REDNESS AT A SITE OF DRUG INJECTION OR IV		
Did you HAVE ANY PAIN, SWELLING, REDNESS AT A SITE OF DRUG INJECTION OR IV?		
O Yes	O No	O Not Applicable

POUNDING OR RACING HEARTBEAT (PALPITATIONS)				
How OFTEN did you feel a POUNDING OR RACING HEARTBEAT (PALPITATIONS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your POUNDING OR RACING HEARTBEAT (PALPITATIONS)? at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

BED SORES	
Did you have any BED SORES?	
O Yes	O No

UNABLE TO HAVE AN ORGASM OR CLIMAX			
Were you UNABLE TO HAVE AN ORGASM OR CLIMAX?			
O Yes	O No	O Not sexually active	O Prefer not to answer

TOOK TOO LONG TO HAVE AN ORGASM OR CLIMAX			
Did you feel that it TOOK TOO LONG TO HAVE AN ORGASM OR CLIMAX?			
O Yes	O No	O Not sexually active	O Prefer not to answer

PROBLEMS WITH CONCENTRATION				
What was the SEVERITY of your PROBLEMS WITH CONCENTRATON at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS	
Did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?	
O Yes	O No

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

RINGING IN YOUR EARS				
What was the SEVERITY of RINGING IN YOUR EARS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

SHIVERING OR SHAKING CHILLS				
How OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

SKIN CRACKING AT THE CORNERS OF YOUR MOUTH				
What was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

SPOTS OR LINES (FLOATERS) THAT DRIFT IN FRONT OF YOUR EYES	
Did you have any SPOTS OR LINES (FLOATERS) THAT DRIFT IN FRONT OF YOUR EYES?	
O Yes	O No

STRETCH MARKS	
Did you have any STRETCH MARKS?	
O Yes	O No

UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES)				
How OFTEN did you have UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your UNEXPECTED OR EXCESSIVE SWEATING DURING THE DAY OR NIGHTIME (NOT RELATED TO HOT FLASHES)? at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

TREMORS				
How OFTEN did you have TREMORS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your TREMORS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

UNUSUAL DARKENING OF THE SKIN				
Did you have any UNUSAL DARKENING OF THE SKIN?				
O Yes	O No			

UNUSUAL VAGINAL DISCHARGE				
Did you have any UNUSUAL VAGINAL DISCHARGE?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

URINE COLOR CHANGE				
Did you have any URINE COLOR CHANGE?				
O Yes	O No			

VAGINAL DRYNESS				
What was the SEVERITY of your VAGINAL DRYNESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

HOARSE VOICE				
What was the SEVERITY of your HOARSE VOICE at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

VOICE CHANGES				
Did you have any VOICE CHANGES?				
O Yes	O No			

WATERY EYES (TEARING)				
What was the SEVERITY of your WATERY EYES (TEARING) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did WATERY EYES (TEARING) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING)				
What was the SEVERITY of your WHEEZING (WHISTLING NOISE IN THE CHEST WITH BREATHING) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

PROBLEMS WITH MEMORY				
What was the SEVERITY of your PROBLEMS WITH MEMORY at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PROBLEMS WITH MEMORY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

SKIN BURNS FROM RADIATION					
What was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?					
O None	O Mild	O Moderate	O Severe	O Very severe	O Not applicable

NCI- PRO-CTCAE ITEMS

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No
Please list any other symptoms:	
1.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
2.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
3.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
4.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
5.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
6.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe

Eat 10 Questionnaire[44]

EATING ASSESSMENT TOOL (EAT-10)					
Circle the appropriate response.					
To what extent are the following scenarios problematic for you? 4=Severe problem	0=No problem				
1. My swallowing problem has caused me to lose weight.	0	1	2	3	4
2. My swallowing problem interferes with my ability to go out for meals.	0	1	2	3	4
3. Swallowing liquids takes extra effort.	0	1	2	3	4
4. Swallowing solids takes extra effort.	0	1	2	3	4
5. Swallowing pills takes extra effort.	0	1	2	3	4
6. Swallowing is painful.	0	1	2	3	4
7. The pleasure of eating is affected by my swallowing.	0	1	2	3	4
8. When I swallow food sticks in my throat.	0	1	2	3	4
9. I cough when I eat.	0	1	2	3	4
10. Swallowing is stressful.	0	1	2	3	4
	Total EAT-10				

Penetration-Aspiration Scale[43]

Score Description of Events

1. Material does not enter airway.
2. Material enters the airway, remains above the vocal folds, and is ejected from the airway.
3. Material enters the airway, remains above the vocal folds, and is not ejected from the airway.
4. Material enters the airway, contacts the vocal folds, and is ejected from the airway.
5. Material enters the airway, contacts the vocal folds, and is not ejected from the airway.
6. Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway.
7. Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort.
8. Material enters the airway, passes below the vocal folds, and no effort is made to eject.

Time and Events Table

Assessment/Procedure	Prior to CRT	Weekly during CRT	6-8 weeks after CRT	10-16 weeks after CRT	6 months after CRT	F-U visits every 2-3 months for 2 yrs after CRT, every 6 months for 3 yrs, then yearly^^^	F-U visits every 6 months for 2 yrs after CRT, then yearly
Clinical evaluation	X	X		X		X	
Panendoscopy (if primary unknown)*	X						
Contrasted neck CT (or PET/CT)	X						
Chest x-ray	X						X
Dental evaluation*	X						
Labs: CBC, serum chemistries, liver function tests, pregnancy test (F)	X						
HPV and p16 testing	X						
QOL and PRO assessments (study coordinator) ("Pre/End/Post" online questionnaire) EORTC QLQ-C30 EORTC QLQ-H&N35 PRO-CTCAE	X			X			X
QOL and PRO assessments (study coordinator) ("Weekly" online questionnaire) EORTC QLQ-H&N35 PRO-CTCAE		X**					
NCI-CTCAE (physician)	X	X***		X			X
Modified Barium Swallow and/or FEES^	X		X		X		
EAT-10	X			X			X
Fiberoptic laryngoscopy	X		X^^	X^^		X	
PET/CT				X			
Thyroid function							X

* Strongly recommended, but not required.

** Weeks 3 and 6 only; the pre/end/post online questionnaire will be given in lieu of the weekly questionnaire at last weekly treatment.

*** Weeks 3 and 6 only

^ This should be quantified with the Rosenbek Penetration Aspiration Scale

^^ Laryngoscopy required at only one of these timepoints (i.e., 6 weeks or 12 weeks post-CRT)

^^^ Exact timing of follow-up visits is flexible based on physician's standard of care

Version 10/19/2016